SUPPORT FOR THE AMENDMENTS

Claim19 has been amended for clarity and to recite that the "composition comprises at most 0.5% by weight of gabapentin lactam;" that the nonacidic cation "is selected from the group consisting of alkali metals, alkaline earth metals, and mixtures thereof;" and that the anion of a mineral acid "is selected from the group consisting of fluoride, chloride, bromide, iodide, sulfate, phosphate, and mixtures thereof." Support for amended Claim 19 can be found in Claims 19, 30, and 34, as originally filed, and on page 5, lines 20-24, of the specification. Claims 20-28, 31, 34-37, 57, 59, and 61 have been amended for clarity. Accordingly, support for amended Claims 20-28, 31, 34-37, 57, 59, and 61 can be found in the same claims, as previously presented.

Applicants have also added new Clams 74-85. Support for new Claim 74 can be found in Claim 37, as originally filed. Support for new Claim 75 can be found in Claim 31, as originally filed, and on page 4, line 28, of the specification. Support for new Clams 76-85 can be found on page 5, lines 20-24, of the specification.

No new matter has been added. Claims 19-29, 31, 34-37, 56-64, and 74-85 are pending in this application.

REMARKS

Present Claims 19-29, 31, 34-37, and 74-85 relate to compositions, which comprise gabapentin and at least one salt of a nonacidic cation and an anion of a mineral acid, in which the composition comprises more than 20 ppm of the anion of a mineral acid, based on the amount of the gabapentin. The claimed compositions also comprise at most 0.5% by weight of gabapentin lactam. Moreover, the nonacidic cation is "selected from the group consisting of alkali metals, alkaline earth metals, and mixtures thereof," and the anion of a mineral acid

"is selected from the group consisting of fluoride, chloride, bromide, iodide, sulfate, phosphate, and mixtures thereof."

Claims 56-64 relate to various methods of using the presently claimed compositions.

The present inventors have discovered that the presently claimed compositions are surprisingly stable despite the presence of a high amount of an anion of a mineral acid, such as chloride. Simply put, it is the surprising discovery of the present inventors that gabapentin may be stabilized against the formation of the corresponding lactam in the presence of an anion of a mineral acid by the addition of a nonacidic cation which is an alkali metal and/or an alkaline earth metal.

The cited references contain no disclosure or suggestion of the presently claimed compositions or methods. Moreover, these references contain no suggestion of the unexpected advantages afforded by the presently claimed compositions. Accordingly, these references cannot affect the patentability of the present claims.

The rejection of Claims 1-18 under 35 U.S.C. §103(a) in view of U.S. Patent No. 6,054,482 (Augart et al) in view of U.S. Patent No. 4,024,175 (Satzinger et al) and U.S. Patent No. 5,693,845 (Jennings et al) has been obviated by the cancellation of these claims. Thus, the rejection should be withdrawn.

The rejection of Claims 19-28 and 30-37 under 35 U.S.C. §103(a) in view of U.S. Patent No. 6,531,509 (Singer et al) in view of Satzinger et al and Jennings et al; and the rejection of Claim 29 under 35 U.S.C. §103(a) in view of Singer et al in view of Satzinger et al and Jennings et al and in further view of Augart et al are respectfully traversed. As explained in Augart et al:

> The lactams display a certain toxicity and must, therefore, be avoided as far as possible. For example, gabapentin has a toxicity (LD_{50}, mouse) of more than 8000 mg/kg, for the corresponding lactam (VI) a toxicity of 300 mg/kg. Consequently, these impurities and the potential formation of such decomposition products during

> storage of pharmaceutical compositions must be reduced to a minimum for reasons of safety.

Augart et al, at col. 4, lines 50-57.

> In order not to exceed the upper limit of 0.5% by weight of gabapentin lactam (referred to the gabapentin), which is regarded as being permissible, and in order to ensure the storage stability not only of the active material but also of the corresponding pharmaceutical forms of preparation, the following procedures are to be maintained:
>
> > 1. The active materials of formula (I) must be prepared as highly purified, nonderivatized free amino acids, for example, from the corresponding hydrochloride by ion exchange. The proportion of remaining hydrochloride admixtures should thereby not exceed 20 ppm. The same also applies to other mineral acids.

Augart et al, at col. 5, lines 18-29.

Thus, Augart et al teach that it is necessary to reduce the amount of the hydrochloride to below 20 ppm in order to suppress the formation of the undesirable gabapentin lactam.

Singer et al describes the teaching of Augart et al as follows:

> According to Augart, because the lactam has a higher toxicity than gabapentin, its presence in gabapentin should be limited if not eliminated. To combat lactam formation and provide product stability, Augart stresses the importance of (i) starting with gabapentin raw material that contains 0.5% or less of corresponding lactam, ***(ii) not allowing the anion of a mineral acid in the composition to exceed 20 ppm***, and (iii) using a specifically selected adjuvant that is not adverse to gabapentin stability.

Augart et al, at col. 1, line 64, to line 2, line 6, emphasis added.

However, Singer et al goes on assert:

> It has now been found that Augart's reliance on maintaining the anion of a mineral acid as not exceeding 20 ppm is misplaced. Thus, gabapentin and pharmaceutical formulations of gabapentin can be prepared and stored such that initially they do not contain more than 0.5% of the lactam, and even after one year of storage at 25°C. and 60% atmospheric humidity, the conversion of gabapentin to its corresponding lactam does not exceed 0.2% by weight of gabapentin. That is, gabapentin and pharmaceutical formulations of gabapentin have been found to be stable even though such formulations do not meet Augart's requirements (ii) and (iii).

Singer et al, at col. 2, lines 23-34.

However, in fact, Singer et al actually only exemplifies the use of quaternary amines and other bases to stabilize gapapentin against the formation of the corresponding lactam in the presence of chloride anions. For example, all of Examples 1-4 and 7-11 involve the use of tributylamine, Example 5 employs trihexylamine, and Example 6 uses tripropylamine. In Examples 12 and 13, sodium methoxide and sodium bicarbonate are added, respectively. Examples 14 and 15 employ tetramethylammonium hydroxide and in tetrabutylammonium hydroxide, respectively. Example 16 uses sodium tetraborate but is irrelevant, because the chloride content is only 10 ppm, *i.e.*, less than 20 ppm. Examples 17-19 use the products of Examples 1, 2, and 4, respectively, which all involved the use of tributyl amine.

Thus, on close inspection, it is seen that Singer et al actually only discloses the use of a trialkylamine or some other type of base to stabilize gabapentin in the presence of high amounts of chloride. Satzinger et al and Jennings et al merely disclose that gabapentin can form pharmaceutically acceptable salts. There is no teaching in any of the cited references which would even remotely suggest that gabapentin could be stabilized against the formation of the corresponding lactam in the presence of an anion of a mineral acid, such as chloride, by the addition of a nonacidic cation, which is an alkali metal and/or an alkaline earth metal.

In contrast, present Claims 19-29, 31, 34-37, and 74-85, as amended, are directed toward compositions which comprise a salt of a nonacidic cation and an anion of mineral acid, in which the nonacidic cation is an alkali metal and/or an alkaline earth metal, and contain more than 20 ppm of the anion of a mineral acid. Moreover, present Claims 19-29, 31, 34-37, and 74-85, as amended, also recite that the compositions comprise at most 0.5% by weight of gabapentin lactam. It is the surprising discovery of the present inventors that it is not necessary to add a trialkylamine or some other type of base to stabilize gabapentin in the presence of an anion such as chloride. Instead, stability may be conferred by the addition of a nonacidic cation, such as an alkali metal and/or an alkaline earth metal.

In support of the assertion, that the present compositions are stable, Applicants cite the results of Examples 3 and 4, which are shown in Figs. 3 and 4. For comparison, the Examiner's attention is directed toward Examples 1 and 2, the results of which are given in Figs. 1 and 2. Certainly, there is no teaching in any of the cited references which would even remotely suggest the stability afforded by the presently claimed compositions.

For these reasons, the rejection should be withdrawn.

The objection to Claims 29-34 has been obviated by appropriate amendment. As the Examiner will note, these claims have been amended such that they are free of the criticisms outlined on page 2 of the Office Action. Thus, the objection should be withdrawn.

The rejection of Claims 13 and 14 under 35 U.S.C. §112, second paragraph, has been obviated by the cancellation of these claims. Accordingly, the rejection should be withdrawn.

Applicants submit that the present application is now in condition for allowance, and early notification of such action is earnestly solicited.

Respectfully submitted,

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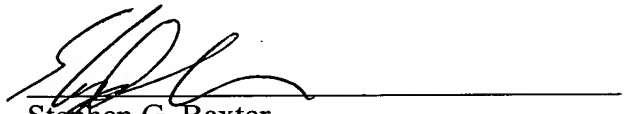

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